

Bioinformatics

CS300

**Domains according
to UniProt and String**

Week12, Deck 1

Fall 2022

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Proteins Fold Into Specific Structures for Functionality

Nucleation, Rapid Folding, and Globular Intrachain Regions in Proteins

Donald B. Wetlaufer

Wetlaufer, Donald B. "Nucleation, rapid folding, and globular intrachain regions in proteins." *Proceedings of the National Academy of Sciences* 70.3 (1973): 697-701.

Abstract

Distinct structural regions have been found in several globular proteins composed of single polypeptide chains. The existence of such regions and the continuity of peptide chain within them, coupled with kinetic arguments, suggests that the early stages of three-dimensional structure formation (nucleation) occur independently in separate parts of these molecules. A nucleus can grow rapidly by adding peptide chain segments that are close to the nucleus in aminoacid sequence. Such a process would generate three-dimensional (native) protein structures that contain separate regions of continuous peptide chain. Possible means of testing this hypothesis are discussed.

Different regions in same protein (*domains*) performing specific tasks.



Structures For Functions





One Car, Many Functions



Windows to allow driver to see out while driving

Ventilation for cooling

Headlights to illuminate the road when driving at night

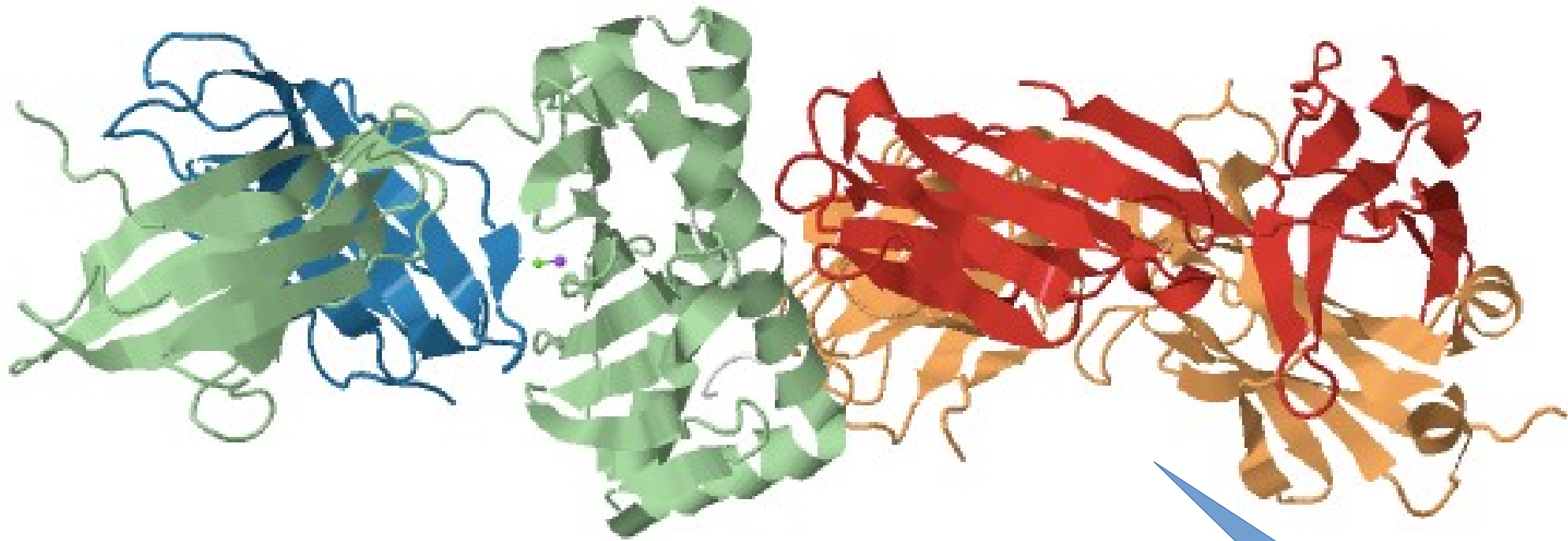
License plate: for Identification

Door to allow driver to enter the car

Wheels, necessary for mobility



Proteins Also Have Specific Functional Regions, Too!



Protein Data Bank:
5WLG

Click! This is
a link!

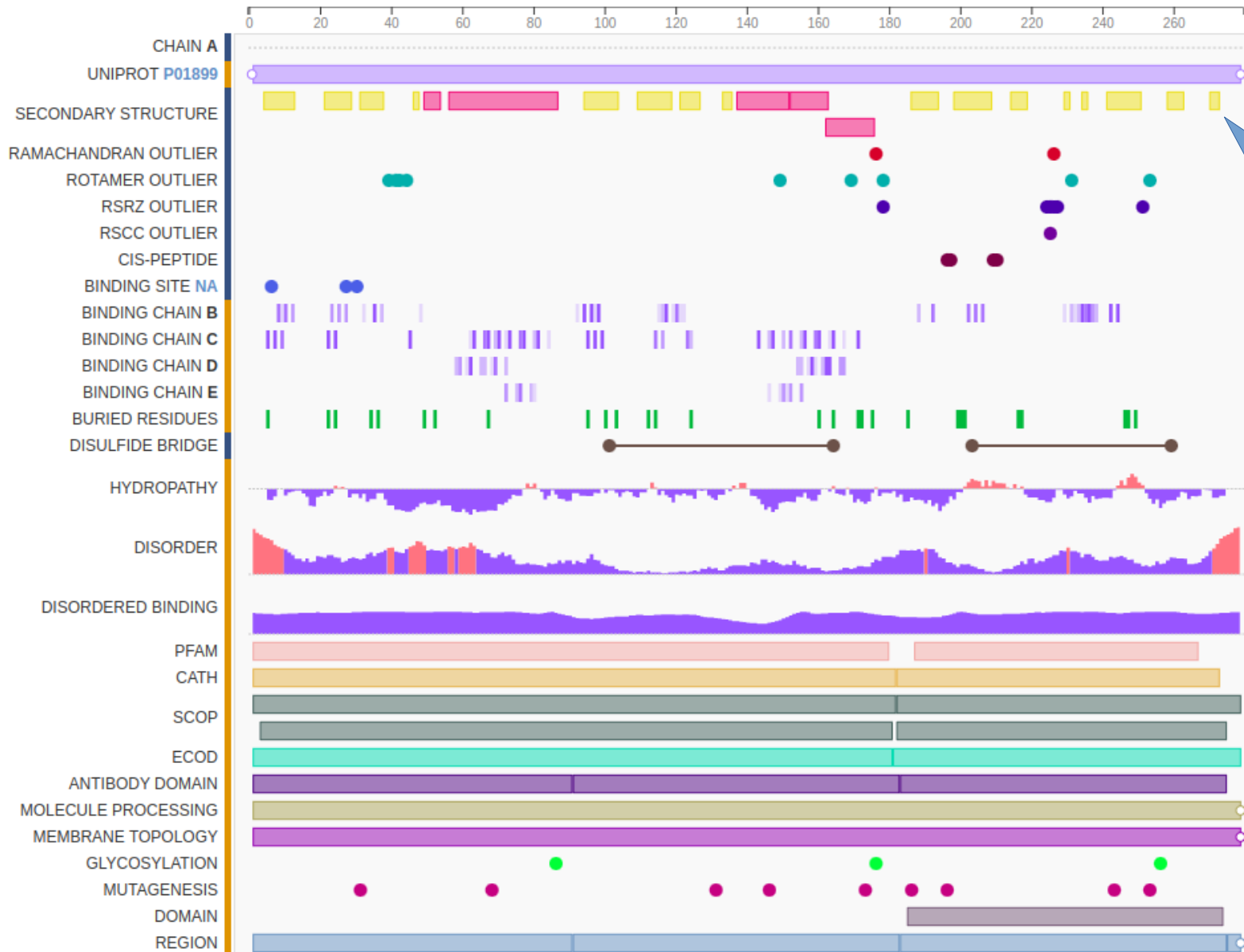


Crystal Structure of H-2Db with the GAP501 peptide (SQL)

Chain

A

H-2 class I histocompatibility antigen, D-B alpha chain - Mus musculus



See the
locations
of
Coils,
Sheets,
Helices,
Turns

Domains

- A protein **domain** is a conserved part of a given protein sequence and (tertiary) structure.
- Can evolve, function, and exist independently of the rest of the protein chain
- Each domain forms a compact three-dimensional structure
- Often can be independently stable and folded.

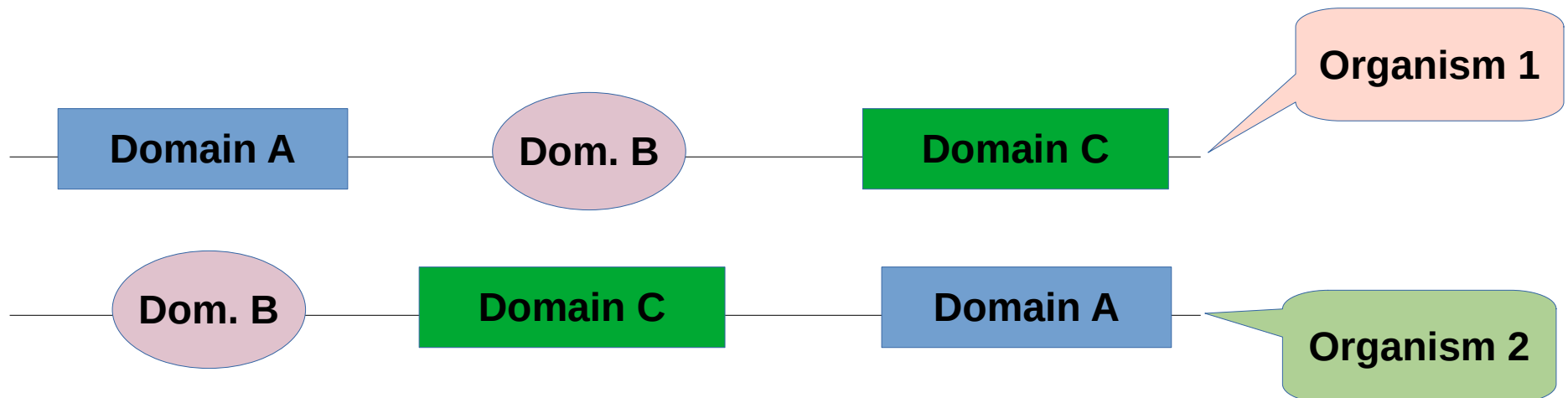


SMART domain 'bubblegram' for human fibroblast growth factor (FGF) receptor 1 (type P11362 into web site: smart.embl.de)



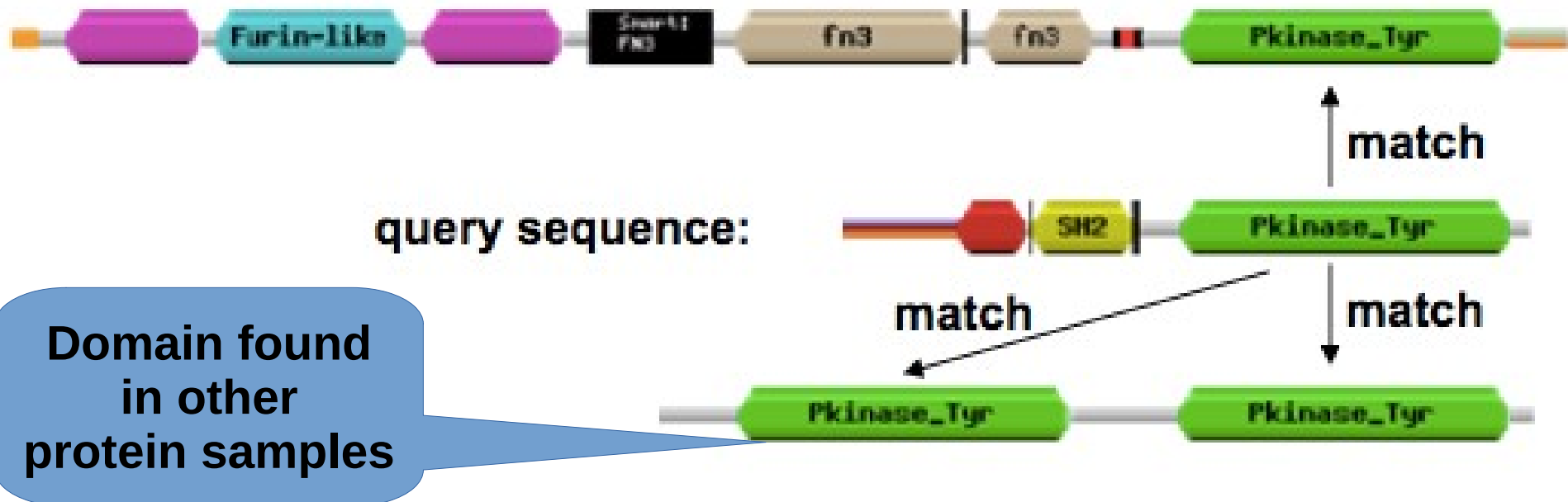
Domain Synteny

- A different order of domains in genomes
- Could provide information about relatedness across genome samples.
- Article: *Domain team: synteny of domains is a new approach in comparative genomics*
 - <https://pubmed.ncbi.nlm.nih.gov/18025683/>



Finding a Domain?

- Alignment across proteins may show domains
- Use databases to align and match protein subsections
 - [Pfam](#), [Smart](#), [Interpro](#) and other database tools





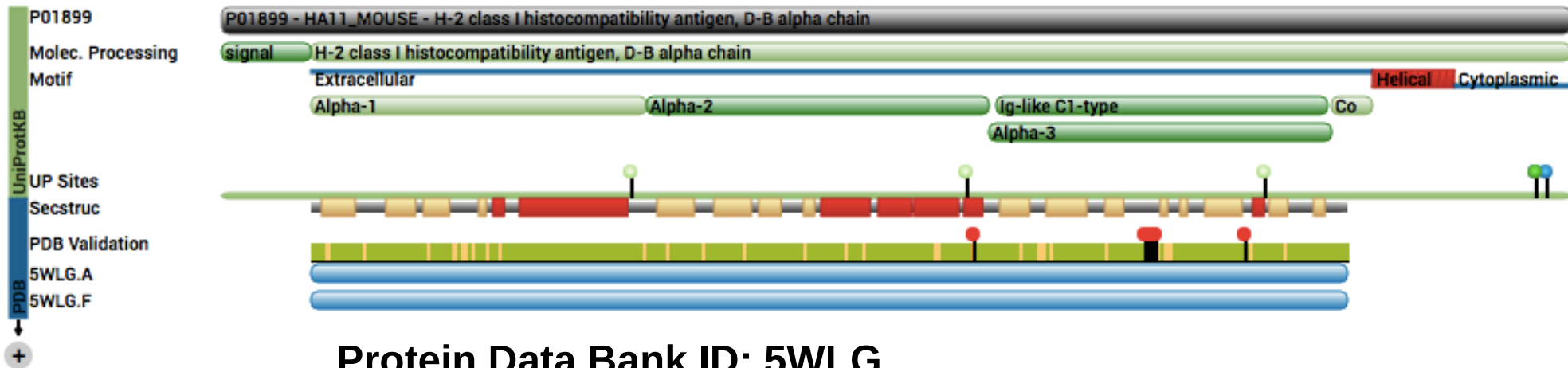
Alignment?!

- Provide more info about a protein's family, relatedness and other details.
- Domain landmarks include: low-complexity or disorder to suggest that these regions may have a specific syntax or pronounced grammar.

```
A5ASC3.1 14 SIKLWPPSQTTRALLVERHANNLST..PSIFTRK..YGLSKEEARENAKQIEEVACSTANQ.....HYEKEPDGDDGSSAVQLYAKECSKLILEVLK 101
B4F917.1 13 SIKLWPPSESTRIMLVDRHTNNLST..ESIFSRK..YRLLGKQEAHENAKTIEELCFALADE.....HFREEPDGDDGSSAVQLYAKETSKHMLEVLK 100
A9S1V2.1 23 VFKLWPPSGQTRERVRQKHALKLS..ACFESQS..FARIELADAQEHARAIEEVAFGAQE.....ADSGGDKTGSAMVWYAKHASKLMLETLR 109
B9GSN7.1 13 SVKLWPPGOSTRLMLVERHTKNFIT..PSFISRK..YGLLSKEEAEEDAKTIEEVAFARANO.....HYEKOPDGDGSSAVQIYAKESSRLMLEVLK 100
Q8H056.1 30 SESIWPPTQRTDRAVVRRLVDTLGG..DTILCKR..YGAVPAADAEPARGIEAEAFDAAA..SGEAAATASVEEGIKALQYSKEVSRRLDFVK 120
Q004Z3.2 44 SLSIWPPTSQRTDRAVVRRLVDTLVA..PSILSKR..YGAVPEACAGRAAAVEAEAYAVTES..SSAAAAPASVEDGIEVLQAYSKEVSRRLLELAK 135
B9MMW8.1 56 SFSIWPPTQRTDRAIISRLIETLST..TSVLSKR..YGTIPKEEASEASRIIEEAFSGAST.....VASSEKDGLEVLQLYSKEISKRMLETVK 141
Q0IYC5.1 29 SFAWPPTRRTDRAVVRRLVAVLSGDTTALAKRYR..YGAVPAADAERAARAVEADAFDASA.....SSSSSSSVEDGIEVLQLYSREVSRRLAFVR 121
A9NW46.1 13 SIKLWPPSESTRMLVERHTONLSS..VSFFSRK..YGLLSKEEARENAKRIEETAFLANO.....HEAKEPNLDSSVQFYAREASKLMLEALK 100
Q9C500.1 57 SLRIWPPTQKTRDAVLNRLIETLST..ESILSKR..YGTLKSDATTYAKLIEEAYGVASH.....AVSSDDGDIKILELYSKEISKRMLESVK 142
Q2HRI7.1 25 NYSIWPBKQRTDRAVKNRLIETLST..PSVLTKR..YGTMSADEASAARIQIEDEAFSVANA.....SSSTSNQNVITILEVYSKEISKRMLETVK 110
Q9M7N3.1 28 SFKIWPPTQRTREAVVRRLVETLTS..QSVLSKR..YGVIPEDATSAARIIEEAFSVASV..ASASTGGRPEDEWIEVLHIYSQEIQRVESAK 119
Q9M7N6.1 25 SESIWPPTQRTDRAVINRLIESLST..PSILSKR..YGTLPQDEASETARLIEEAFARAGS.....TASDADGGIEILQVYSKEISKRMIDTVK 110
Q9LE82.1 14 SVIOWPPSKSTRMLVERHTKNITT..PSIFSRK..YGLLSVEEAEQDAKRIEDLAFATANK.....HFQNEPDGDDTSAMVWYAKESSKLMLEVLK 101
Q9M651.2 13 SIKLWPPSLPTRKALIERITNNFSS..KTIFTEK..YGLSKQDQATENAKRIEDIAFSTANQ.....QFEREPDGDGSSAVQLYAKECSKLILEVLK 100
B9R748.1 48 SLSIWPPTQRTDRAVITRLIETLSS..PSVLTKR..YGTISHDEAESARRIEDEAFGVANT.....ATSAEDDGLEILQLYSKEISRRMLDTVK 133
```

Domains By PDB

- Domains give the protein special qualities:
 - Domain Names: *Alpha1*, *Alpha2*, *Alpha3*, *Ig-like C1-type*



- This protein:
 - <https://www.rcsb.org/pdb/explore/explore.do?structureId=5WLG>
- Domains:
 - <https://www.rcsb.org/Annotations/5WLG>
- Help with features
 - <https://www.rcsb.org/pages/help/featureView>



Domains By Uniprot

- Domains give the protein special qualities:
 - Domain Names *Alpha1 (and etc.) can be Blasted to find copies in other proteins*

Family & Domainsⁱ

Domains and Repeats

Feature key	Position(s)	Description	Actions	Graphical view	Length
Domain ⁱ	209 – 297	Ig-like C1-type	Add BLAST		89

Region

Feature key	Position(s)	Description	Actions	Graphical view	Length
Region ⁱ	25 – 114	Alpha-1	Add BLAST		90
Region ⁱ	115 – 206	Alpha-2	Add BLAST		92
Region ⁱ	207 – 298	Alpha-3	Add BLAST		92
Region ⁱ	299 – 309	Connecting peptide	Add BLAST		11

UniProt ID: P01899

A Protein Knowledge Base

http://www.uniprot.org/uniprot/P01899#family_and_domains

Click! This is
a link!



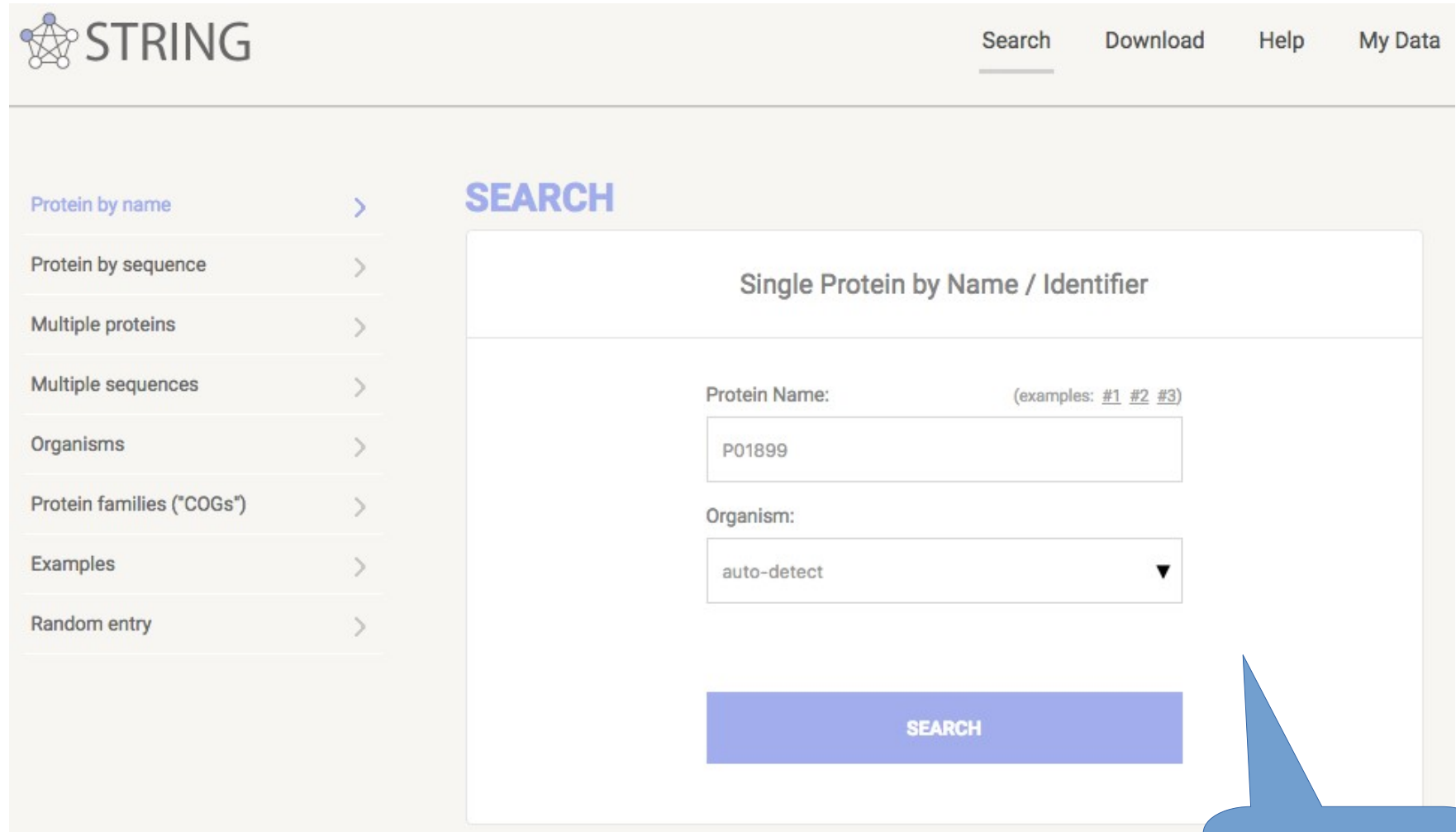
ALLEGHENY
COLLEGE

Bring the Tool!



Up Next!

STRING: Functional Protein Association Networks



The screenshot shows the STRING database search interface. On the left is a sidebar with navigation links: "Protein by name", "Protein by sequence", "Multiple proteins", "Multiple sequences", "Organisms", "Protein families ("COGs")", "Examples", and "Random entry". The main area is titled "SEARCH" and contains a form for "Single Protein by Name / Identifier". The form has two input fields: "Protein Name:" with the value "P01899" and "Organism:" with a dropdown menu set to "auto-detect". A blue "SEARCH" button is at the bottom of the form. The top of the page has a navigation bar with links for "Search", "Download", "Help", and "My Data".

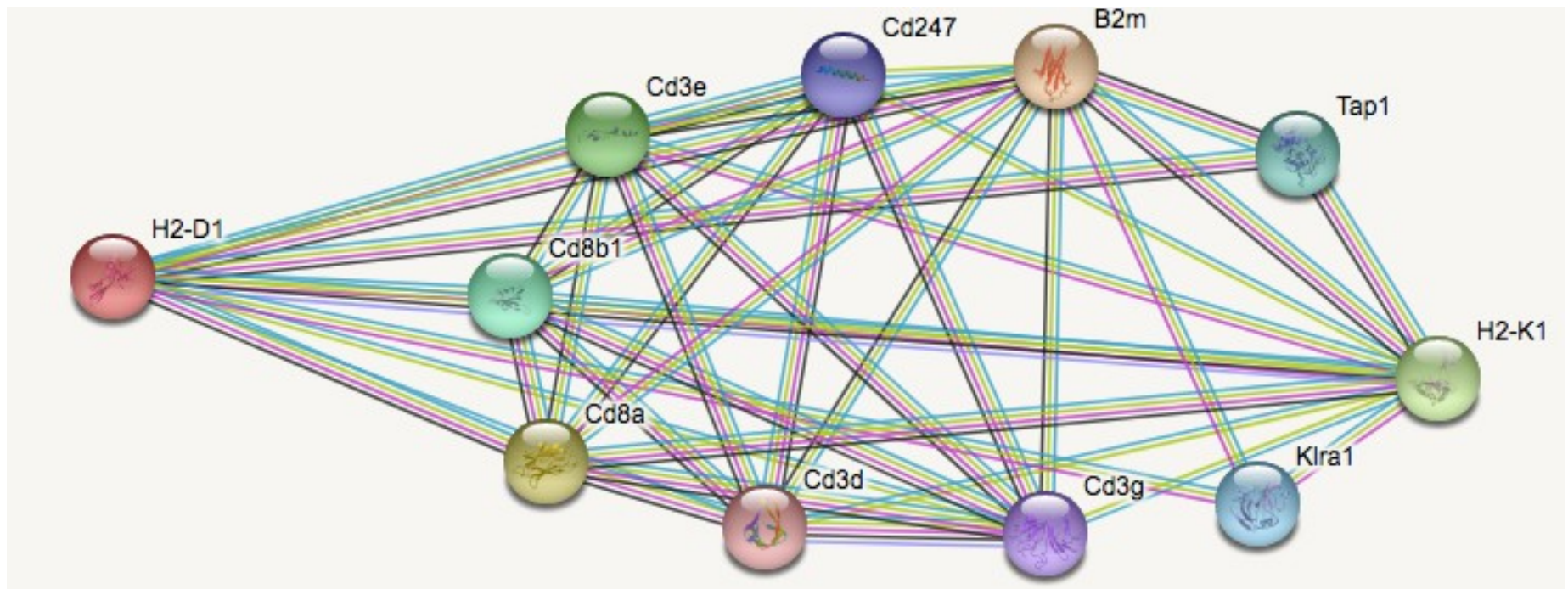
String DB ID P01899

<http://string-db.org/>

Click! This is
a link!

STRING: Functional Protein Association Networks

- Known and predicted protein-protein interactions
- How does a protein interact with others?
- What types of interactions are these (across all known genomes, of any organism)?



STRING: Functional Protein Association Networks

- What types of interactions are happening and where?

Network Stats

number of nodes: 11
number of edges: 29
average node degree: 5.27
avg. local clustering coefficient: 0.877

expected number of edges: 11

PPI enrichment p-value: 6.46e-06

your network has significantly more interactions than expected (what does that mean?)

Functional enrichments in your network

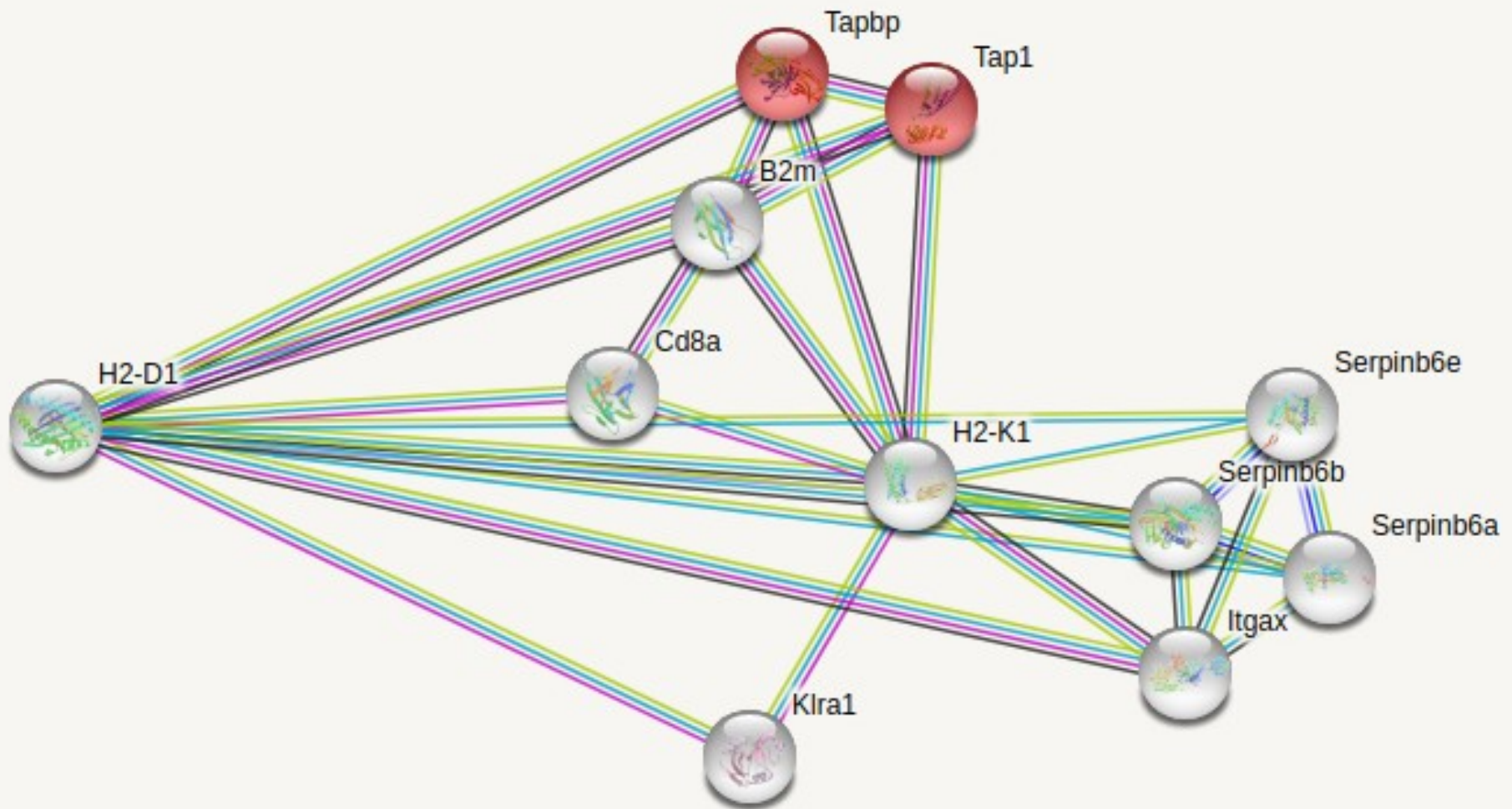
Note: some enrichments may be expected here (why?)

[explain columns](#)

> Biological Process (Gene Ontology)				
<u>GO-term</u>	<u>description</u>	<u>count in network</u>	<u>strength</u>	<u>false discovery rate</u>
GO:0002479	antigen processing and presentation of exogenous peptide a...	2 of 2	3.3	2.43e-05
GO:0019885	antigen processing and presentation of endogenous peptide ...	5 of 7	3.16	2.52e-12
GO:0002485	antigen processing and presentation of endogenous peptide ...	2 of 3	3.13	3.57e-05

STRING: Functional Protein Association Networks

- These nodes play roles in the interaction.



STRING: Functional Protein Association Networks

- Click on an edge to see the type of interaction

Interaction

● H2-D1 [ENSMUSP00000134570]

H-2 class I histocompatibility antigen, D-B alpha chain; Involved in the presentation of foreign antigens to the immune system; Belongs to the MHC class I family



● B2m [ENSMUSP00000099534]

Beta-2-microglobulin; Component of the class I major histocompatibility complex (MHC). Involved in the presentation of peptide antigens to the immune system; Belongs to the beta-2-microglobulin family

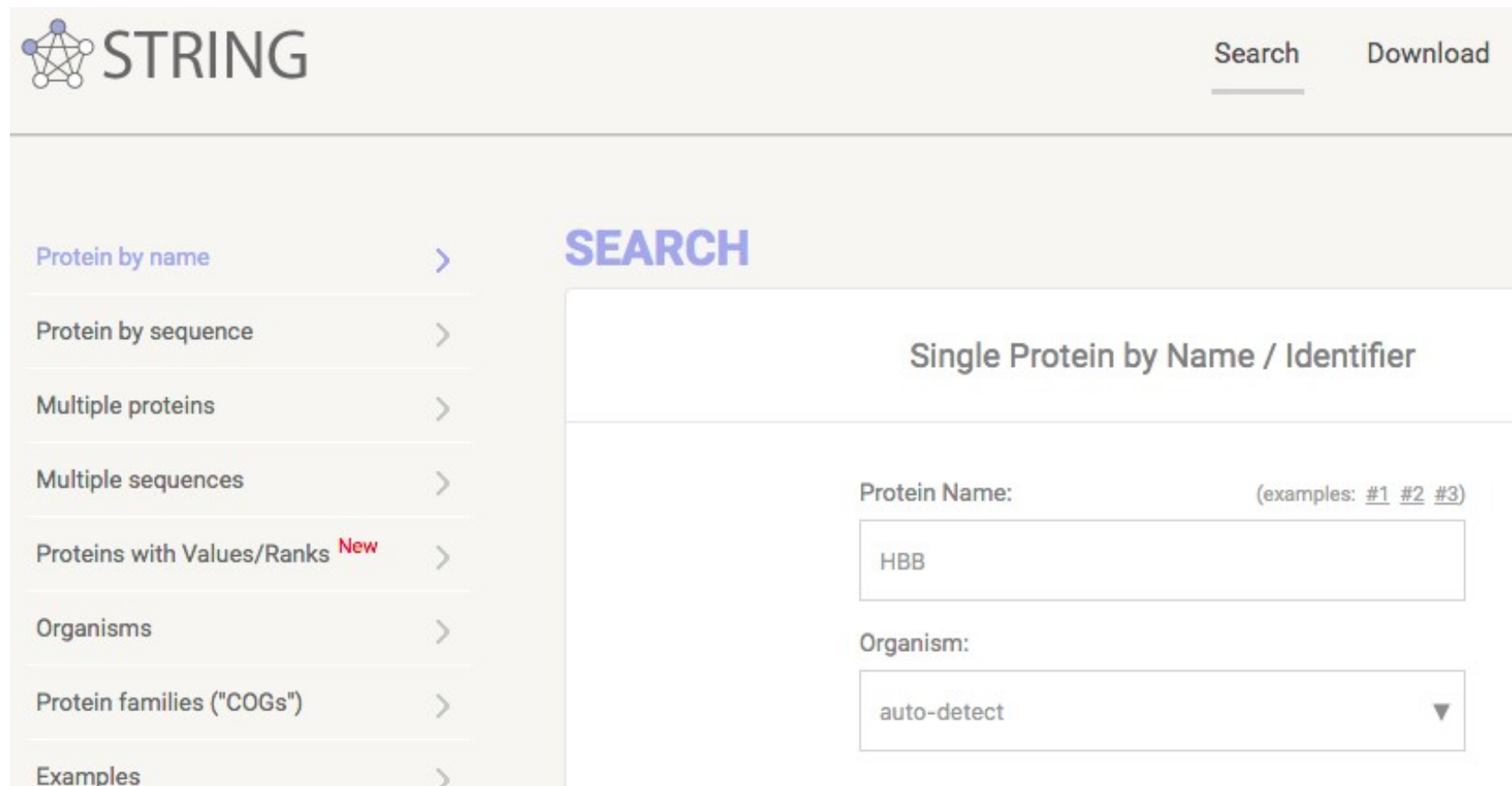
Evidence suggesting a functional link:

Neighborhood in the Genome:	none / insignificant.	
Gene Fusions:	none / insignificant	
Cooccurrence Across Genomes:	none / insignificant	
Co-Expression:	yes (score 0.582). In addition, putative homologs are coexpressed in other organisms (score 0.061).	Show
Experimental/Biochemical Data:	yes (score 0.903). In addition, putative homologs were found interacting in other organisms (score 0.405).	Show
Association in Curated Databases:	yes (score 0.900).	Show
Co-Mentioned in Pubmed Abstracts:	yes (score 0.650). In addition, putative homologs are mentioned together in other organisms (score 0.081).	Show

Combined Score: 0.999

STRING: Functional Protein Association Networks

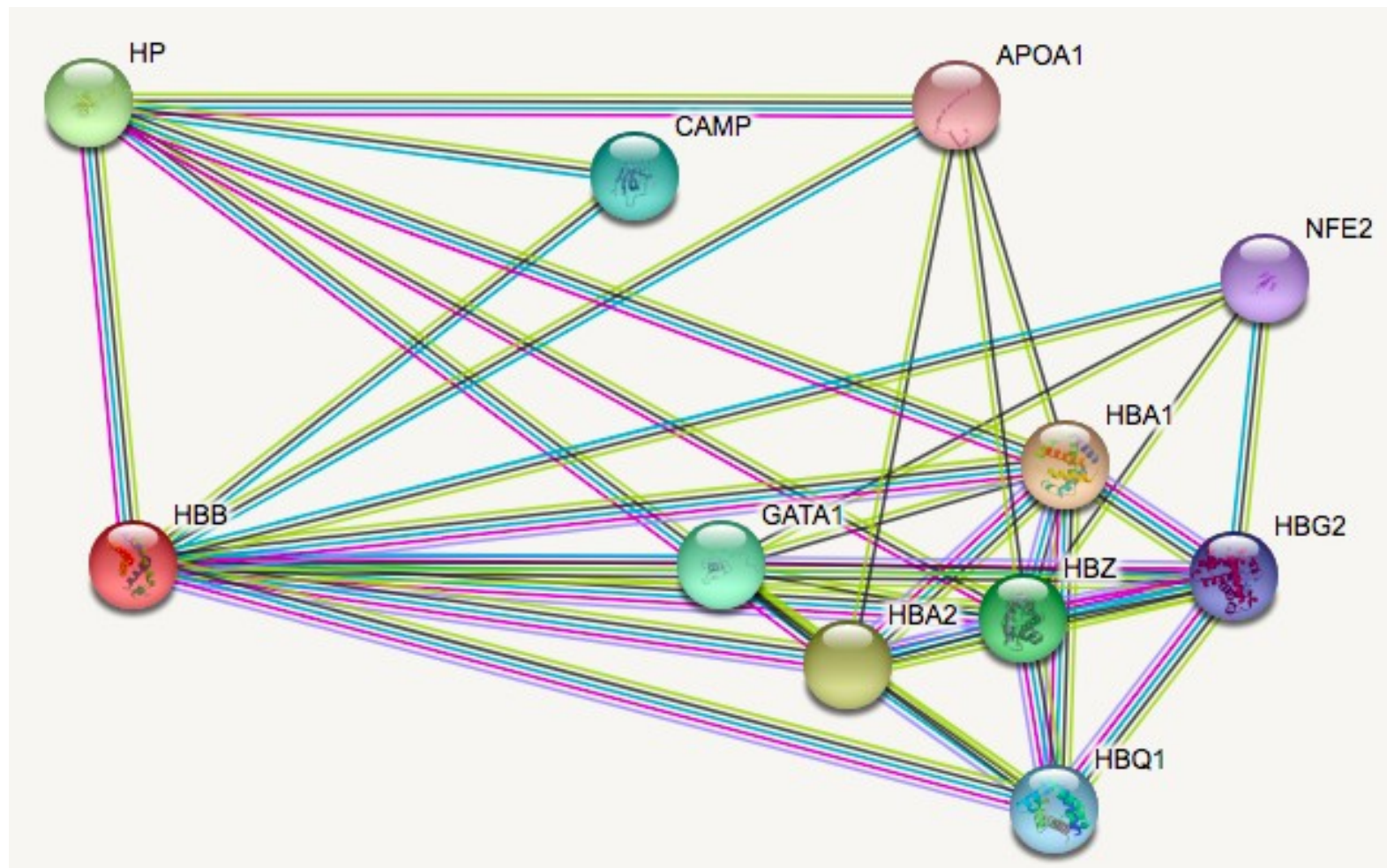
- Question: What proteins (from genes) interact with **HBB** protein (from the gene)?



The screenshot shows the STRING database search interface. On the left is a sidebar with navigation links: "Protein by name", "Protein by sequence", "Multiple proteins", "Multiple sequences", "Proteins with Values/Ranks" (marked as "New"), "Organisms", "Protein families (\"COGs\")", and "Examples". The main area is titled "SEARCH" and contains a section "Single Protein by Name / Identifier". This section has two input fields: "Protein Name:" with the example text "(examples: #1 #2 #3)" and a text box containing "HBB"; and "Organism:" with a dropdown menu currently set to "auto-detect".

STRING: Functional Protein Association Networks

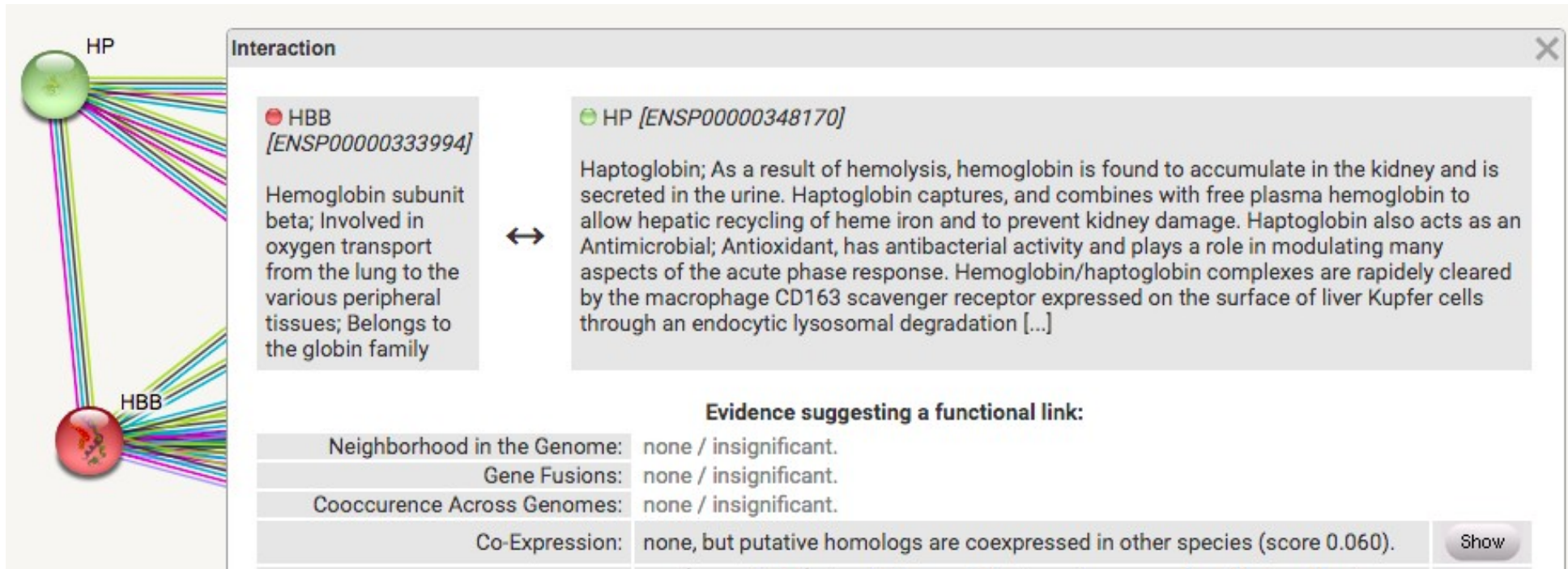
- Answer: Lots!



<https://string-db.org/>

STRING: Functional Protein Association Networks

- What kinds of interactions?



The image shows a screenshot of the STRING database interface. On the left, a network diagram shows two nodes, HP (green) and HBB (red), connected by multiple colored lines representing different types of interactions. The main window displays the details for the interaction between HBB and HP.

Interaction

HBB [ENSP00000333994]
Hemoglobin subunit beta; Involved in oxygen transport from the lung to the various peripheral tissues; Belongs to the globin family

HP [ENSP00000348170]
Haptoglobin; As a result of hemolysis, hemoglobin is found to accumulate in the kidney and is secreted in the urine. Haptoglobin captures, and combines with free plasma hemoglobin to allow hepatic recycling of heme iron and to prevent kidney damage. Haptoglobin also acts as an Antimicrobial; Antioxidant, has antibacterial activity and plays a role in modulating many aspects of the acute phase response. Hemoglobin/haptoglobin complexes are rapidly cleared by the macrophage CD163 scavenger receptor expressed on the surface of liver Kupfer cells through an endocytic lysosomal degradation [...]

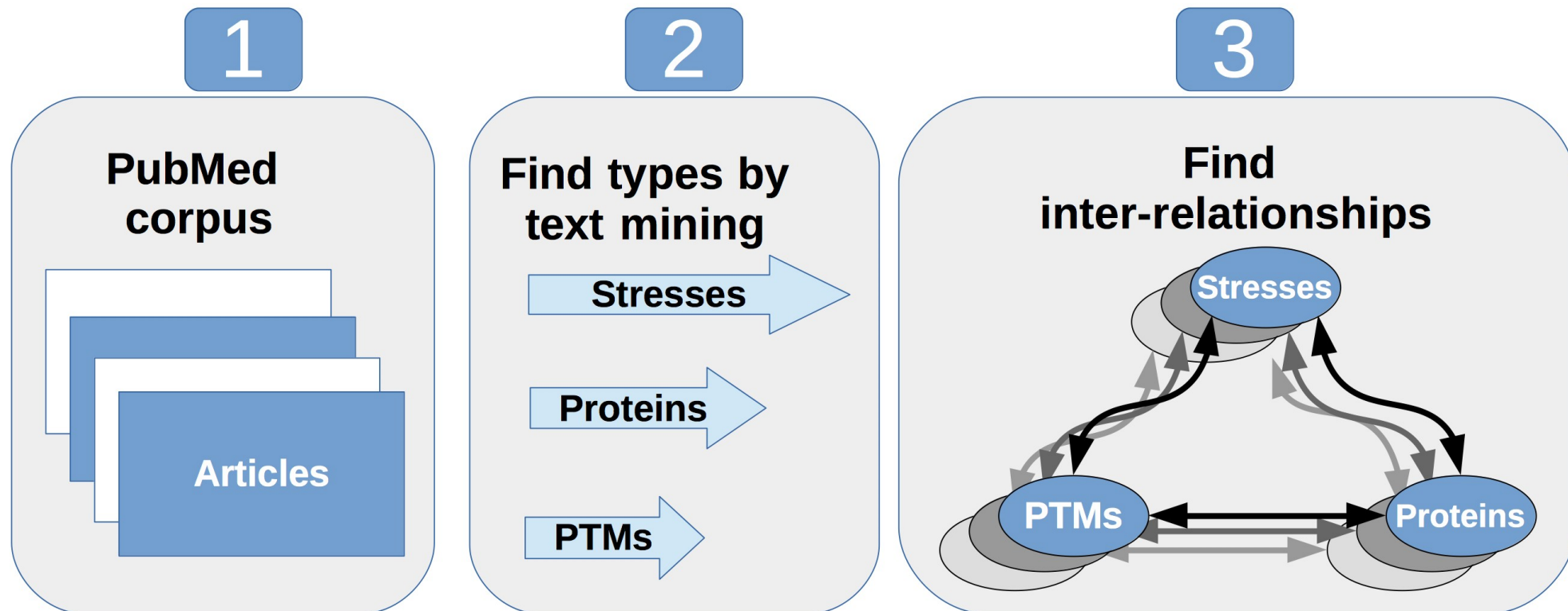
Evidence suggesting a functional link:

Neighborhood in the Genome:	none / insignificant.
Gene Fusions:	none / insignificant.
Cooccurrence Across Genomes:	none / insignificant.
Co-Expression:	none, but putative homologs are coexpressed in other species (score 0.060).

Show

Criteria to Determine Relations

- There are many ways to measure the distance between two different proteins
 - Text Mining





String: by Text Mining



- HBB's interactions according to the literature
- Go to SETTINGS and select only "Textmining"

Basic Settings

Network type:

- ☒ full network (the edges indicate both functional and physical protein associations)
- ☐ physical network (the edges indicate that the proteins are part of a physical complex)

meaning of network edges:

- ☒ evidence ( line color indicates the type of interaction evidence)
- ☐ confidence ( line thickness indicates the strength of data support)

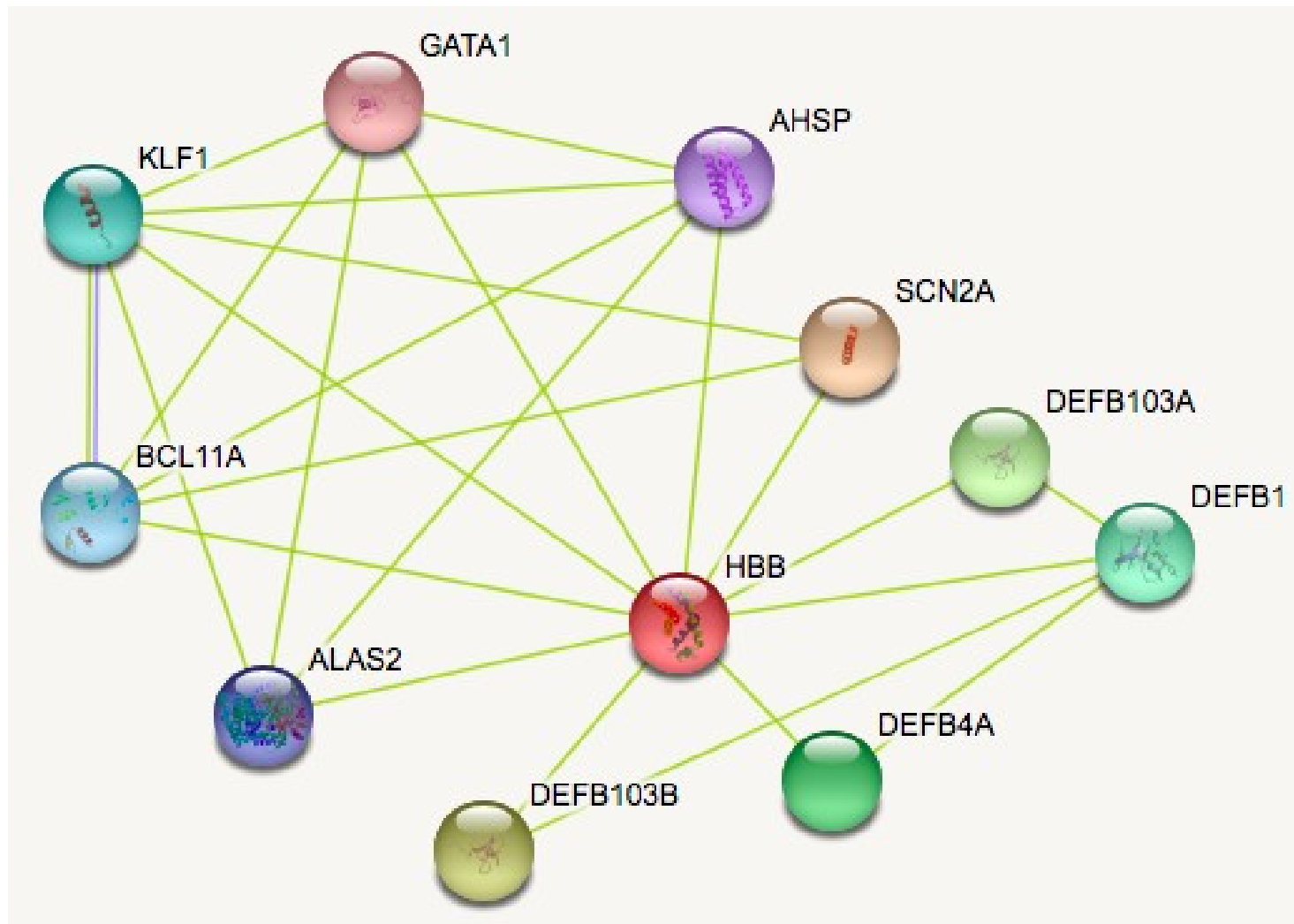
active interaction sources:

- ☒ Textmining ☐ Experiments ☐ Databases ☐ Co-expression
- ☐ Neighborhood ☐ Gene Fusion ☐ Co-occurrence

UPDATE

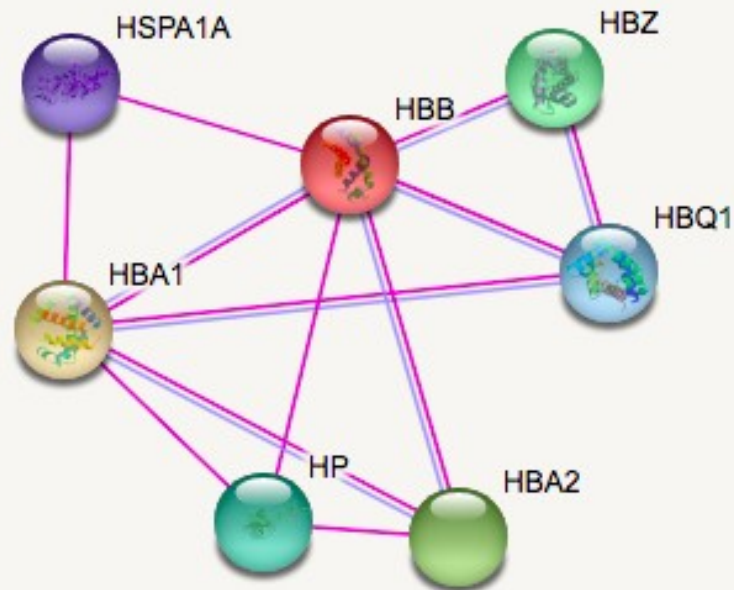
String: by Text Mining

- HBB's interactions according to the literature



String: Linked Experimentally

- Experiments performed to show that protein are related



Interaction

● HBB [ENSP00000333994]

Hemoglobin subunit beta; Involved in oxygen transport from the lung to the various peripheral tissues; Belongs to the globin family



● HBZ [ENSP00000252951]

Hemoglobin subunit zeta; The zeta chain is an alpha-type chain of mammalian embryonic hemoglobin



String: Linked Experimentally

- Learn about the experiments

LAB EXPERIMENTS

Relevant datasets in *Mus musculus*:

protein-protein interaction (intact) <i>Detected by psi-mi:"MI:0027"(cosedimentation) assay</i>	● H2-D1 ● B2m [... and 1527 other proteins]
protein-protein interaction (mint) <i>Detected by psi-mi:"MI:0027"(cosedimentation) assay</i>	● H2-D1 ● B2m [... and 1527 other proteins]
protein-protein interaction (dip) <i>Detected by x-ray crystallography assay</i>	● H2-D1 ● B2m
protein-protein interaction (intact) <i>Detected by psi-mi:"MI:0114"(x-ray crystallography) assay</i>	● H2-D1 ● B2m



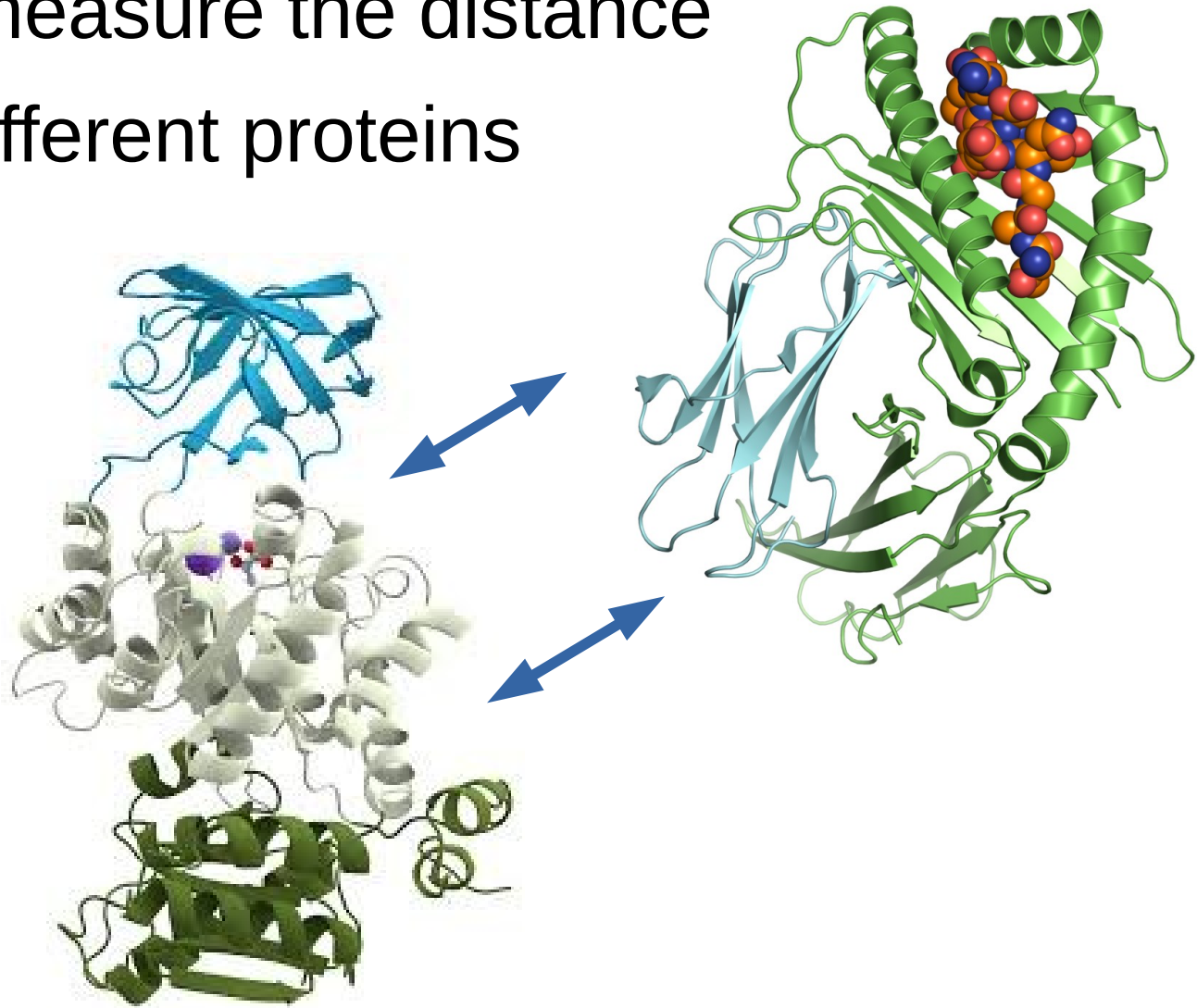
Global survey of organ and organelle protein expression in mouse: combined proteomic and transcriptomic profiling.

▼ Kislinger T, Cox B, Kannan A, Chung C, Hu P, Ignatchenko A, Scott MS, Gramolini AO, Morris Q, Hallett MT, Rossant J, Hughes TR, Frey B, Emili A
Cell. 125(1):173-86 (2006).



Criteria to Determine Relations

- Other ways to measure the distance between two different proteins
 - Neighborhood
 - Experiments
 - Databases
 - Co-Expression
 - And others...





More Information?

- Unify the representation of gene and gene product attributes across all species information
 - **AmiGO 2: Gene ontology**
 - <http://amigo.geneontology.org/amigo/landing>
- Information of effects of genetic variation on human health
 - **Genetics Home Reference**
 - <https://ghr.nlm.nih.gov/>

Go Play!

- Pick your favorite protein and get gene name
 - <http://www.uniprot.org/>
example: P01899, gene name: H2-D1
- Then check out its networks at:
- <https://string-db.org/>

Play

